J. med. Genet. (1964). 1, 95.

A Boy with XXXXY Sex Chromosomes*

M. C. JOSEPH, JANET M. ANDERS, and ANGELA I. TAYLOR

From the Department of Paediatrics, Guy's Hospital, and the Paediatric Research Unit, Guy's Hospital Medical School

Eight patients with XXXXY sex chromosomes are on record (Fraccaro, Kaijser, and Lindsten, 1960; Miller, Breg, Schmickel, and Tretter, 1961; Fraser, Boyd, Lennox, and Dennison, 1961; Fraccaro, Klinger, and Schutt, 1962; Barr, Carr, Pozsonyi, Wilson, Dunn, Jacobson, and Miller, 1962; Pfeiffer, 1962; Schade, Schöller, and Töberg, 1963). In addition two similar patients with a mosaic pattern have been reported (Anders, Prader, Hauschteck, Schärer, Siebermann, and Heller, 1960; Harnden and Jacobs, 1961). We here describe a further patient with XXXXY sex chromosomes in whom congenital heart disease, mental deficiency, dwarfism, abnormal genitalia, and an unusual facies were present.

Case Report

Family History. Both parents were 32 years old when the patient was born, and both are healthy. He has three maternal aunts and two maternal uncles, all healthy. All except one aunt are married and have normal children. His father was an only child. There was no consanguinity between his parents or grandparents. His maternal grandmother had 'heart valve disease'. He has one sister aged 4 years who is well.

Patient's History. (J. A., P.R.U. 877). The mother had toxaemia of pregnancy. After a labour lasting 50 hours, the patient was delivered by breech at term and weighed 4 lb. 12 oz. (2154 g.) He was severely shocked and was nursed in an incubator for the first few days following delivery. His subsequent physical and mental progress was slow and at 5 years of age his height and weight were below the third percentile and his I.Q. was 40 (Merrill-Palmer). He has had two attacks of gastro-enteritis and several episodes of bronchitis with wheeze. A cardiac murmur was first heard at the age of 3 months. He has no symptoms referable to his heart except moderate exercise intolerance.

Physical Examination. At 5 years of age the patient (Fig. 1) weighed 28 lb. (12.7 kg.) (less than third percentile) and was 38 in. (95 cm.) tall (less than third percentile). His appearance (Fig. 2 and 3) re-

* Received December 31, 1963

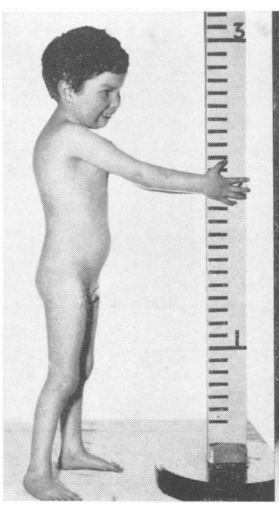

FIG. 1. J. A. aged 5 years.

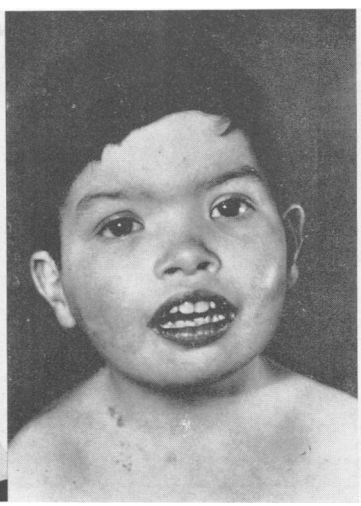

FIG. 2. Facies of J. A. aged 5 years.

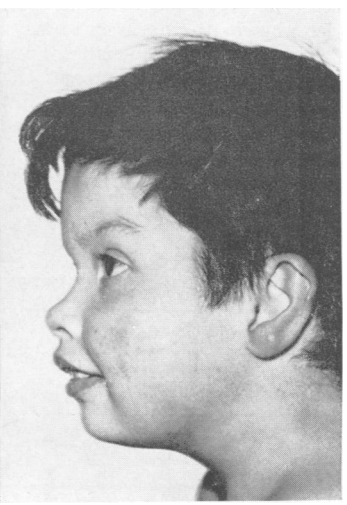

FIG. 3. Facies of J. A. aged 5 years.

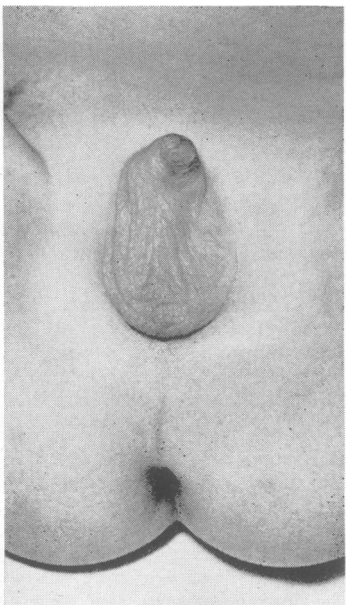

FIG. 4. Scrotum of J. A. aged 6 years.

sembled an oriental with a slight downward and medial slant of the palpebral fissures. He had widely set eyes with epicanthic folds which did not merge with his upper eyelid. The bridge of the nose was flat and the upper eyelids were prominent. The eyebrows were delicately arched and there was excess hair at the side of the face in front of his ears. The helix of the right ear was small and that of the left prominent. The occiput and the cephalic index (0.76) were normal. He had a rather short neck with a suggestion of webbing which, however, appeared to be filled in with muscle. The nipples were small. There was a high dorsal kyphosis. The palmar creases on the left hand almost ran into each other. Both fifth fingers were incurved. There was limitation of hand supination and pronation on both sides. His skin, especially on the legs, was rather rough. The empty scrotum (Fig. 4) was small, slightly pigmented, rugose, surrounded by two grooves, and had a midline raphe. The penis was small and the perineum rather large and flat. Some of these features are seen in the patients described by Laurance (1961) and in 13–15 (D_1) trisomy. The gonads could not be palpated in the inguinal canals or perineum. Both sides of the chest bulged, the left more than the right. There was no cyanosis and no clubbing. The cardiac impulse was felt both in the fourth left space near the sternum and in the region of the left nipple. A systolic thrill was felt in the fourth left space. The first sound was followed by an ejection click, the second sound was loud and single, and there was a Grade 3/6 systolic murmur along the left sternal border, which was well heard at the apex and in the axilla, and a Grade 2 diastolic rumble at the apex conducted into the axilla. There were no signs of failure. Other systems were normal.

Investigations. His haemoglobin was 10.9 g. (70%). The total white count was 13,200 cells per c.mm. with 59% polymorphs and 35% lymphocytes. The urine was normal. Radiographs of the radio-ulnar joints showed synostosis and the iliac index was 54° (mean at one year 79° ± 8). The bone age was that of a 2½-year-old male. Histology of the skin showed a slight increase in collagen. The total ridge count was 141 (mean 145 ± 51 in males, Holt, 1961), and the maximal *atd* angles were 86° (Table I and Fig. 5) (mean at this age is 88° ± 16, Penrose, 1954). Details of his blood groups and those of his parents are shown in Table A in the Appendix.

The electrocardiogram showed broad P waves in lead I and peaked P waves in V_1 suggesting left and right atrial enlargement. Biventricular hypertrophy was present. The chest radiograph showed cardiomegaly and increased pulmonary vasculature. Phonocardiography confirmed the auscultatory findings. Cardiac catheterization revealed mitral incompetence, a small atrial septal defect, and right ventricular pressure at about systemic level (the pulmonary artery was not entered). Retrograde aortography and left ventricular angiography demonstrated a large patent duct and confirmed the presence of mitral incompetence. The right outflow tract was normal. At operation (Sir Russell Brock) a large patent ductus was ligated and divided. The patient made an uninterrupted recovery.

TABLE I

RIDGE COUNTS (RADIAL COUNTS ON RIGHT, ULNAR ON LEFT)

	Ridge Count											Maximal *atd* Angles	
	Right Hands					Left Hands						Right	Left
	I	II	III	IV	V	I	II	III	IV	V	Totals		
J. A.	**16–11**	**0–3**	**13–24**	**22–9**	**15–0**	**13–7**	**5–0**	**11–12**	**22–9**	**12–0**	141	46°	40°
Mrs A.	**16–0**	**0–0**	**15–0**	**16–0**	**15–0**	**13–0**	**0–0**	**12–0**	**12–0**	**4–0**	103	38.5°	46.5°
Mr A.	**17–0**	**10–23**	**22–21**	**22–17**	**18–4**	**12–0**	**13–15**	**18–18**	**22–16**	**20–0**	189	39°	38°

Note: The bold figures are those used for the total ridge count.

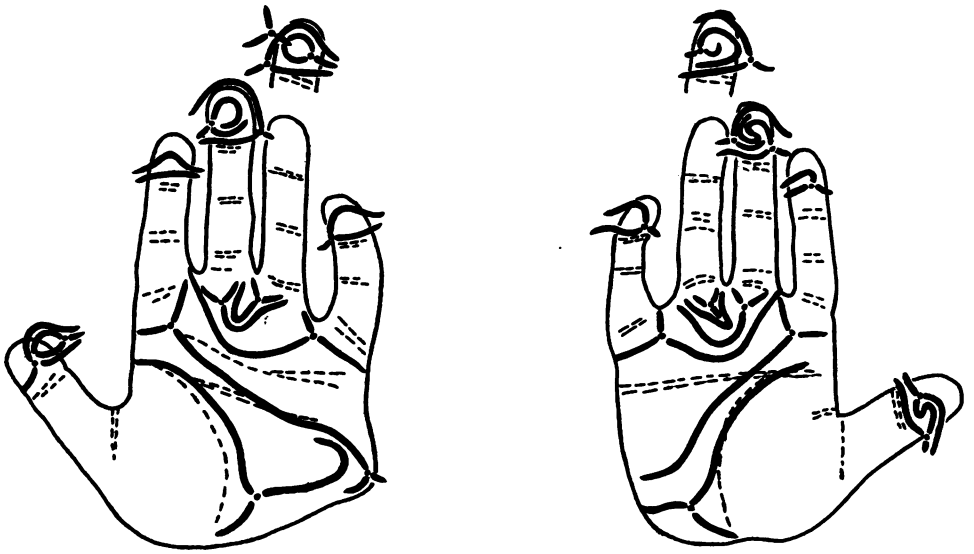

FIG. 5. Triradii and main lines of the dermal ridges in J. A.

Cytology. The incidence of sex chromatin in oral mucosal cells and cultured cells is shown in Table II. Cells with one, two, and three peripheral sex chromatin masses were observed in both tissues.

Satisfactory blood smears were taken on two occasions. On the first occasion one drumstick was found in 807 polymorphs. On the second occasion two drumsticks were found in 3,300 polymorphs. The reason for the very low incidence on both occasions is unknown but a similar low incidence in an XXXXY patient was reported by Fraccaro *et al.* (1962). No double or other multiple drumsticks were seen.

The results of chromosome counts made on slides prepared from two peripheral blood cultures and a single skin culture are given in Table III. The modal number is 49. The cells with less than this number appeared broken. Analysis of three karyotypes showed five chromosomes in the 21–22–Y group, the majority of cells having a clear Y chromosome, and 18 chromosomes in the X–6–12 group instead of 15 as would be expected in a normal male.

Dr. F. Giannelli labelled the cells from skin culture with tritiated thymidine during the latter part of the DNA synthetic period and subsequently examined them by autoradiography. Three chromosomes in the X–6–12 group showed differential uptake of tritiated thymidine as compared with the remainder of the chromosome set. Thus, though the X chromosomes cannot be individually identified by morphological means alone, the presence of three additional members of the X–6–12 group together with the finding of three sex-chromatin bodies in a proportion of cultured and oral mucosa cells, and the results of labelling with tritiated thymidine, suggest that the additional members are X chromosomes, giving a chromosome constitution of 2A + XXXXY (A = haploid autosome set).

Discussion

Table IV shows the prominent features in the 8 previously described patients and our own. It can be seen from this Table that these patients have a wide variety of abnormalities. The most

TABLE II

PERCENTAGE DISTRIBUTION OF PERIPHERAL SEX-CHROMATIN MASSES

No. of Peripheral Masses	Oral Mucosa (300 cells)	Cultured Skin (200 cells)
0	33	28
1	29	39
2	27	32
3	11	6

TABLE III

CHROMOSOME COUNTS

	Chromosome Counts					
Type of Culture	46	46	47	48	49	>49
Blood 1	—	—	—	1	14	—
Blood 2	—	—	—	1*	20	—
Skin	1*	—	2*	4*	49	—

* Broken cells.

TABLE IV

MAIN FEATURES IN PREVIOUSLY DESCRIBED PATIENTS AND PRESENT CASE (J. A.)

Features	Present	Absent	Not Reported
Male phenotype	9	—	—
'Dysmaturity'	4	2	3
Dwarfism	3	4	2
Abnormal facies	7	1	1
Squint	3	5	1
Epicanthic folds	3	—	6
Widely set eyes	6	—	3
Down and medial slant of palpebral fissures	4	1	4
Flat occiput	3*	1	5
Cleft palate	2	4	3
Short neck	3	—	6
Abnormal spine	4	1	4
Incurved fifth finger	6	—	3
Radio-ulnar synostosis	5	1	3
Small scrotum	8	1	—
Impalpable gonads	6	3	—
Small penis	7	1	1
Mental retardation	9	—	—
Congenital heart disease	2†	7	—
Dry skin	3	—	6
Retarded bone age	5	—	4
Low iliac index	1	—	8
Abnormal palm prints	1	1	7

* Includes brachycephaly (1).
† Both have patent ductus arteriosus.

consistent features include mental retardation, abnormal facies and genitalia, and skeletal changes.

Maternal and paternal age, parity, gestational age, and birth weights are shown in Table V. Consanguinity, pregnancy, previous history, and illness in sibs do not appear to be significant and have not been included in Table V. The family history of the patient, described by Miller *et al.* (1961), of lymphatic leukaemia in the father, and a paternal aunt and paternal cousin both having regular Down's syndrome, is interesting in view of the association of leukaemia and Down's syndrome (Krivit and Good, 1957; Stewart, Webb, and Hewitt, 1958; Holland, Doll, and Carter, 1962).

TABLE V

SOME GESTATIONAL DATA

Reference	Maternal Age (yr.)	Paternal Age (yr.)	Parity	Birth Order	Gestational Age	Birth Weight (g.)
Fraccaro *et al.* (1960)	23	29	2	1	Term	2380
Miller *et al.* (1961)	23	32	3	—	—	—
Fraser *et al.* (1961)	22	24	3	1	—	—
Fraccaro *et al.* (1962)	26	29	2	2	Term	3175
Barr *et al.* (1962) Case 1	25	24	3	1	Term	2550
Barr *et al.* (1962) Case 2	38	38	4	4	Term	3288
Pfeiffer (1962)	20	23	1	1	Term	1190
Schade *et al.* (1963)	28	27	2	1	—	3089
Present case	32	32	2	1	Term	2154

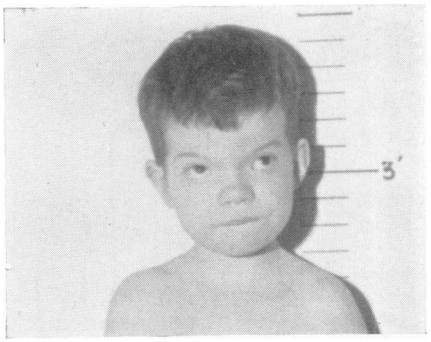

FIG. 6. Facies of Case 1 reported by Barr *et al.* (1962).

Mental Retardation. All except one patient who was reported as 'probably retarded' and another two as 'retarded' showed severe retardation, the I.Q. figures being 40, 35, 30, 21, and 20.

The Facies. This was definitely abnormal in some way in seven patients. The abnormal features varied, but included epicanthic folds, widely set eyes, and slanting of the palpebral fissures. The occiput was flat in two patients, and in one the head was described as brachycephalic. The facies of our patient closely resembled that of Case 1 reported by Barr *et al.* (1962) (Fig. 6) and, allowing

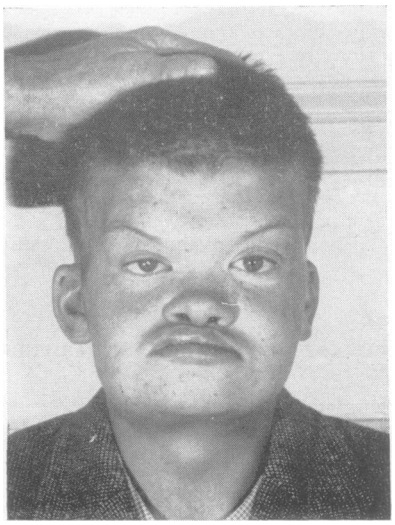

FIG. 7. Facies of patient reported by Schade *et al.* (1963).

for the age difference, also resembled the patient reported by Schade *et al.* (1963) (Fig. 7).

The Genitalia. These were consistently abnormal, the penis being small, the gonads impalpable, or the scrotum small. In the three specimens examined histologically the testis showed reduction or absence of germ cells (at ages 7 months, 7 years, and 8 years.

Skeletal Changes. The spine showed kyphosis, lordosis, and an extra lumbar vertebra in four patients, and radio-ulnar synostosis in five patients. The latter has also been described in an XXXY male (Ferguson-Smith, Johnston, and Handmaker, 1960). Six of the patients showed incurving of the fifth finger.

Palm and Fingerprints. Details of these are shown in Table I and Fig. 5, and in Fig. A and B in the Appendix. Unlike the patient reported by Fraccaro *et al.* (1962) the number of arches and small loops was not increased and the total ridge counts were near the mean.

Other Features. A striking feature in four patients was their light weight in relation to term, their weights being 2 lb. 10 oz. (1190 g.), 4 lb. 12 oz. (2154 g.), 5 lb. 4 oz. (2380 g.), and 5 lb. 10 oz. (2550 g.) at term. This has been referred to as dysmaturity (Sjöstedt, Engleson, and Rooth, 1958) or intrauterine growth retardation (Warkany, Monroe, and Sutherland, 1961). Other patients with chromosomal anomalies, notably those with trisomy 17–18 (E_1) and 13–15 (D_1) (Paul E. Polani, 1963, personal communication), show this dysmaturity. Congenital heart disease was present in our patient and that of Fraccaro *et al.* (1960), and the anatomical defect was the same, namely patent ductus arteriosus.

Summary

A 5-year-old boy with XXXXY chromosomes is reported. The main features included dwarfism, abnormal genitalia, unusual facies, mental deficiency, patent ductus arteriosus, and radio-ulnar synostosis. These features are compared with those in other reported patients.

We thank Prof. Paul E. Polani for analysis and interpretation of the dermatoglyphics, Mr. John L. Hamerton for his help, Dr R. C. Mac Keith who originally saw the patient, Sir Russell Brock for the operative findings, Mrs C. Dawbarn for the illustrations of the palm prints, and the Photographic Department. We also thank Dr. Ruth Sanger of the Lister Institute for the detailed blood groups. Prof. M. L. Barr and Dr H. Schade very kindly allowed us to reproduce the photographs of their patients (Fig. 6 and 7). This work was supported by The Spastics Society.

References

Anders, G., Prader, A., Hauschteck, E. Schärer, K., Siebenmann R. E., and Heller, R. (1960). Multiples Sex-Chromatin und komplexes chromosomales Mosaik bei einem Knaben mit Idiotie und multiplen Missbildungen. *Helv. paediat. Acta*, **15**, 515.

Barr, M. L., Carr, D. H., Pozsonyi, J., Wilson, R. A., Dunn, H. G., Jacobson, T. S., and Miller, I. R. (1962). The XXXXY sex chromosome abnormality. *Canad. med. Ass. J.*, **87**, 891.

Ferguson-Smith, M. A. Johnston, A. W., and Handmaker, S. D. (1960). Primary amentia and micro-orchidism associated with an XXXY sex-chromosome constitution. *Lancet*, **2**, 184.

Fraccaro, M., Kaijser, K., and Lindsten, J. (1960). A child with 49 chromosomes. *ibid.*, **2**, 899.

——, Klinger, H. P., and Schutt, W. (1962). A male with XXXXY sex chromosomes. *Cytogenetics*, **1**, 52.

Fraser, J. H., Boyd, E., Lennox, B., and Dennison, W. M. (1961). A case of XXXXY Klinefelter's syndrome. *Lancet*, **2**, 1064.

Harnden, D. G., and Jacobs, P. A. (1961). Cytogenetics of abnormal sexual development in man. *Brit. med. Bull.*, **17**, 206.

Holland, W. W., Doll, R., and Carter, C. O. (1962). The mortality from leukaemia and other cancers among patients with Down's syndrome (mongols) and among their parents. *Brit. J. Cancer*, **16**, 177.

Holt, S. B. (1961). Palm-prints and their uses in medical biology. *Cerebr. Palsy Bull.*, **3**, 333.

Krivit, W., and Good, R. A. (1957). Simultaneous occurrence of mongolism and leukemia. Report of a nationwide survey. *Amer. J. Dis. Child.*, **94**, 289.

Laurance, B. M. (1961). Hypotonia, obesity, hypogonadism and mental retardation in childhood. In British Paediatric Association. Proceedings of the thirty-second annual meeting. *Arch. Dis. Childh.*, **36**, 690.

Miller, O. J., Breg, W. R., Schmickel, R. D., and Tretter, W. (1961). A family with an XXXXY male, a leukæmic male, and two 21-trisomic mongoloid females. *Lancet*, **2**, 78.

Penrose, L. S. (1954). The distal triradius *t* on the hands of parents and sibs of mongol imbeciles. *Ann. hum. Genet.*, **19**, 10.

Pfeiffer, R. A. (1962). Beitrag zum Erscheinungsbild der XXXXY-Konstitution. *Z. Kinderheilk.*, **87**, 356.

Schade, H., Schöller, L., and Töberg, G. (1963). Ein Patient mit XXXXY-Chromosomen. *Med. Welt.* (*Stuttg.*), 869.

Sjöstedt, S., Engleson, G., and Rooth, G. (1958). Dysmaturity. *Arch. Dis. Childh.*, **33**, 123.

Stewart, A., Webb, J., and Hewitt, D. (1958). A survey of childhood malignancies. *Brit. med. J.*, **1**, 1495.

Warkany, J., Monroe, B. B., and Sutherland, B. S. (1961). Intrauterine growth retardation. *Amer. J. Dis. Child.*, **102**, 249.

Addendum

Since this paper was completed, an additional patient (N.S., P.R.U. 1528) has been referred by Dr B. Gans to Professor Paul E. Polani. The clinical features were very similar to those of J.A., and he had an identical chromosomal complement. He was the first born of normal parents (father aged 30 years and mother aged 28 years). Gestation was 41 weeks and birth weight 7 lb. 4 oz. (3,288 g.). When seen at 9 years of age, his weight was 46 kg. (more than 97%) and his height 138 cm. (90%). His facies (Fig. 8) was similar to J.A. with widely set eyes, slanting downwards and medially, epicanthic folds, with a wide but otherwise normal bridge of nose. The lower lip was thick. The eyebrows were very arched. The neck was short and broad and there was moderate bilateral webbing. The lower abdomen was prominent and the mons pubis obese;

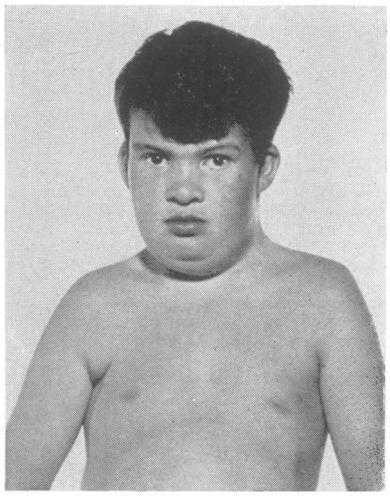

FIG. 8. Facies of N. S. aged 9 years.

the penis was short. The scrotum was rugose and rather flat. A small soft mass was felt in the right scrotum, but no testis was palpable in the left scrotum. Bilateral radio-ulnar synostosis was present. His I.Q. was about 50. He had a persistent ductus arteriosus, which had been ligated in 1959 by Mr D. Waterston at the Hospital for Sick Children, Great Ormond Street. In summary, this boy resembled the pattern of our patient, J.A., and others previously reported, particularly in respect of facies, mental retardation, genitalia, radio-ulnar synostosis, and type of heart defect. The only three patients with a congenital heart defect (Fraccaro *et al.* (1960) and the two reported here) had the same type, namely patent ductus arteriosus. Data on palm and fingerprints are given in the Appendix (Table B). The mother of this boy had a low total ridge count, and the mother of J.A. had a total ridge count below the average. The other point of note in this child was the small number of drumsticks (1 in 1,000), an observation similar to that found in J.A. Details of his blood groups and those of his mother and sister are shown in Table C in the Appendix.

Appendix

TABLE A

BLOOD GROUPS OF J. A., MOTHER, AND FATHER

Name	ABO	MNS	P_1	Rh	Lv^a	K	Le^aLe^b	Fy^aFy^b	Jb^aJb^b	Xg^a
J. A.	B	MsNs	$+^w$	rr	+		—	—		+
Mrs A.	A	NsNs	+	R_2r	±	—	—	+		+
Mr A.	B	MMS	+	R_2r	—	—	—	+		+

TABLE B

RIDGE COUNT OF N. S. AND MRS S. (RADIAL COUNTS ON RIGHT, ULNAR ON LEFT)

	Ridge Counts											Maximal atd Angles	
	Right hands					Left hands					Totals	Right	Left
	I	II	III	IV	V	I	II	III	IV	V			
N. S.	0–0	0–0	0–0	0–0	2–0	0–0	0–0	0–0	0–0	0–0	2	40°	38°
Mrs S.	**9–0**	0–0	0–)	3–0	7–0	**6–0**	0–0	0–0	2–0	3–0	30	39°	55°

Note: The bold figures are those used for the total ridge count.

TABLE C

BLOOD GROUPS OF N. S., MOTHER, AND SISTER

Name	ABO	MN	Rh	K	Xg^a
N. S.	o	MN	R_1R_2	−	+
Mrs S.	o	MM	R_1R_2	−	+
Miss S.	o	MM	R_1R_2	−	+

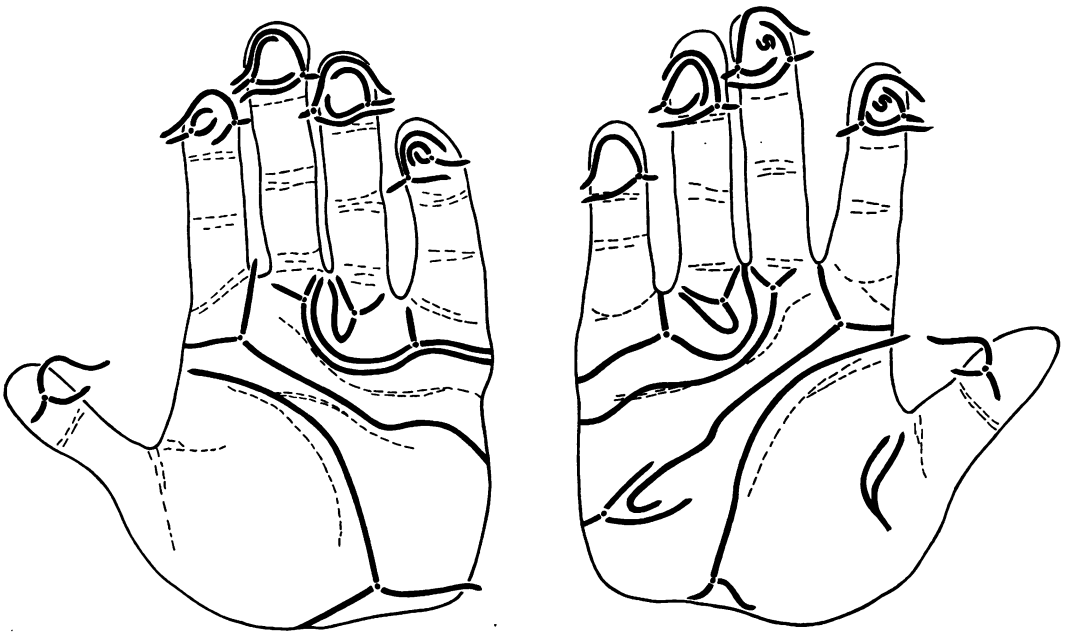

FIG. A. Dermatoglyphics of mother of J. A.

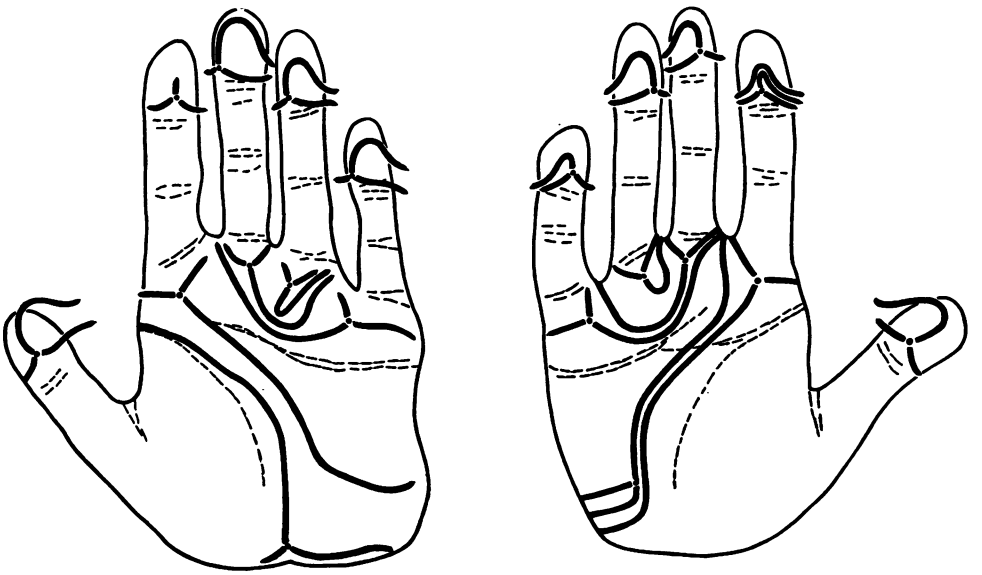

FIG. B. Dermatoglyphics of father of J. A.